

**REMARKS**

Claims 1-19 were pending in the application and are cancelled in the present amendment. New claims 20-31 are presently submitted. Support for new claims 20-31 may be found throughout the specification and it is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

**I. Rejections under 35 U.S.C. § 112, second paragraph**

A. Claims 1 and 18 are rejected under 35 U.S.C. § 112, second paragraph for being indefinite because they allegedly do not set forth the relationship between identical nucleic acids and the fully-matched heterohybrid fragments. Applicants traverse.

Without acquiescing to the propriety of the rejection, and solely to further prosecution, claims 1 and 18 have been canceled. New claim 20 and its dependent claims recite in step (g) "thereby identifying, isolating or separating nucleic acid fragments that are identical between said at least two nucleic acid populations". Applicants assert that this phrase makes it clear that by identifying, isolating or separating the "fully matched heteroduplexes", one is identifying, isolating or separating nucleic acids that are "identical between said at least two nucleic acid populations." Applicants assert that new claim 20 is definite in pointing out and distinctly claiming the subject matter that they regard as their invention.

B. Claims 1, 7 and 11 are rejected under 35 U.S.C. § 112, second paragraph for being indefinite because they allegedly contain a phrase that lack antecedent basis. Applicants traverse. Without acquiescing to the propriety of the rejection, and solely to further prosecution, claims 1, 7 and 11 have been canceled.

C. Claim 13 is rejected under 35 U.S.C. § 112, second paragraph for being indefinite because it contains information in parentheses. Applicants traverse. Without acquiescing to the propriety of the rejection, and solely to further prosecution, claim 13 has been canceled. New claims 20-31 do not contain parentheses.

D. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph for being indefinite because it is allegedly not clear what material is considered to be "MutS-binding material". Applicants traverse. Without acquiescing to the propriety of the rejection, and solely to

further prosecution, claim 16 has been canceled. New claims 20-31 do not recite the phrase “MutS-binding material”.

Accordingly, Applicants respectfully request that these rejections of claims 1, 7, 11, 13, 16 and 18 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn. Applicants submit that new claims 20-31 particularly point out and distinctly claim the subject matter that the Applicants regard as their invention.

## **II. Rejections under 35 U.S.C. § 102(e)**

Claims 1-7, 10-12, 18 and 19 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lin et al. (U.S. Pat. No. 5,871,927, “Lin”). Office Action, page 4 Applicants respectfully traverse.

In order to support an anticipation rejection under 35 U.S.C. § 102, the Examiner must illustrate that each and every element of a claimed invention was disclosed within a single prior art reference. *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990). A claimed invention is anticipated only when it is “known to the art in the detail of the claim.” *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). In other words, not only must the limitations of claim be shown in a single prior art reference, the limitations must be “arranged as in the claim.” *Id.* Lin does not teach or disclose every element of the claimed invention.

The Examiner refers to Figure 3 and Column 8, lines 52-67 of Lin for the alleged teachings that allegedly describe the invention of claim 1. Office Action at page 4. Applicants respectfully disagree. Without acquiescing to the propriety of the rejection, and solely to further prosecution, claims 1-19 are canceled. Applicants will address the rejections in light of new claim 20, and new dependant claims 21-31. In general, Lin relates to methods for the “isolation of desired different sequences from two DNA libraries.” Lin, abstract, lines 2-3. Lin relates to the isolation of the “tester-homohybrid complex” (Lin, column 8, line 63), not the isolation of “fully-matched heteroduplexes”, as recited in new claim 20, step (g). Further, Lin relates to the digestion of single-stranded mismatched ends of the “tester-subtractor heterohybrids” while maintaining the blunt-ended “tester-homohybrids” in Figure 3(b), while new claim 20 step (e) recites the selective digestion of the “perfectly matched blunt-ended homoduplexes by a blunt ended specific nuclease.” Lin therefore does not teach or disclose the isolation of nucleic acid fragments that are identical between at least two

nucleic acid populations, the isolation of fully-matched heteroduplexes, or the digestion of blunt ended homoduplexes by a blunt ended specific nuclease.

Accordingly, Applicants respectfully request that any rejections of claims 1-7, 10-12, 18 and 19 under 35 U.S.C. § 102(e) over Lin be reconsidered and withdrawn. Applicants submit that new claims 20-31 are free of the prior art.

### **III. Rejections under 35 U.S.C. § 103**

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Weissman et al (U.S. Pat. No. 6,287,825, "Weissman") in light of Lin et al. (U.S. Pat. No. 5,871,927). Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. § 103, the USPTO must meet four conditions to establish a prima facie case of obviousness. First, the USPTO must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the USPTO must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the USPTO must show the suggestion, teaching, or motivation to combine the prior art references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Lin does not teach or suggest every element of the invention, Weissman does not make up for this deficiency, and one of skill in the art would not be motivated to combine the teachings of Lin and Weissman.

Without acquiescing to the propriety of the rejection, and solely to further prosecution, claims 1-19 are canceled. Applicants will address the rejections in light of new claims 20-31. New claim 20, and consequently new dependent claims 21-31, recite "digesting perfectly matched blunt-ended homoduplexes by a blunt ended specific nuclease." As explained above, Lin does not teach the digestion of blunt ended homoduplexes by a blunt-end specific nuclease. The Examiner alleges that at column 8, lines 52-56, Weissman discloses "that when the two distinct adaptor molecules are mismatched by the formation of a heterohybrid, they will produce single-stranded (i.e. forked) ends." Office Action at pages 6-7. However,

the Examiner also asserts that “Weissman does not specifically disclose a non-complementary relationship between adaptor molecules at the ends of heterohybrids.” *Id.* at page 8.

Respectfully, the Examiner cannot maintain both positions as they are inapposite.

Further, at column 8, lines 52-56, Weissman relates to the choice of primers for PCR amplification of the DNA, and mismatched DNA strands are not discussed. The Examiner further alleges that Weissman discloses “digesting perfectly matched DNAs by ExoIII (e.g. blunt ended)” at column 1. Office Action at page 7. Respectfully, this is also incorrect. In column 1, Weissman does not relate to the digestion of “perfectly match DNAs by ExoIII”, but rather the digestion of “heterohybrids containing a mismatch.” Weissman, column 1, lines 39-46. Therefore Weissman does not teach or suggest digestion of blunt ended homoduplexes by a blunt-end specific nuclease as recited in new claim 20 and its dependent claims, and Lin does not make up for this deficiency.

Moreover, the Examiner has failed to show any suggestion, teaching, or motivation derived from the references of record to combine the alleged teachings of Lin with the alleged teachings of Weissman produce the methods defined by the present claims. The Examiner has not met the requirement, imposed by the Federal Circuit, that the Examiner make a “clear and particular” showing of the reasons one of ordinary skill in the art would have been motivated to select Lin and Weissman and to combine Lin and Weissman to arrive at the claimed methods. *In re Dembiczak*, at 1617. Indeed, the combination by the Examiner of Lin and Weissman without such a showing has led the Examiner to the “hindsight trap” long criticized by the Federal Circuit. *Id.*

Specifically, one of ordinary skill in the art would not be motivated to combine the teachings of Lin and Weissman. Lin relates to a method for “isolation of different sequences from two DNA libraries” (Lin, abstract) while Weissman relates to a method to isolate “homohybrid or heterohybrid DNA” (Weissman, abstract), which are sequences that are identical from two DNA libraries. Given the diametrically opposed objectives of each method, one of skill in the art would not be motivated to combine Lin and Weissman. Further, the motivation to combine cannot be from the desire to separate heterohybrids from homohybrids by digesting perfectly-matched DNAs by ExoIII (Office Action at page 7) because neither Lin nor Weissman teach or suggest the digestion of perfectly matched DNAs by ExoIII.

New claims 24 and 25 recite “adaptor sequence comprises a recognition site for mut HL”. Regarding new claims 24 and 25, neither Lin nor Weissman teach or suggest an adaptor sequence with a mut HL recognition site, GATC. Weissman at column 1, cited by the Examiner (Office Action at page 8), relates to “heterohybrids containing a mismatch are distinguished from mismatch-free molecules by use of the *E. coli* methyl-directed mismatch repair system” and that “heterohybrids contain DNA strands from different sources”. Weissman, column 1, lines 39-41, and lines 31-32. Applicants respectfully request that the Examiner indicate which lines in column 1 describe the use of an adapter, not source DNA, with a restriction site. Weissman at column 3, cited by the Examiner (Office Action at page 8), relates to “isolating subsets from other, contaminating DNAs by using primers that they attached chemical moieties that can be captured on beads, columns, and the like. In some cases, the DNA is then released by cutting specifically designed sequences in the primers with restriction endonucleases.” Weissman, column 3, lines 8-13.

First, Weissman relates to restriction sites in primers, which used throughout Weissman to mean PCR primers (see, for example, Weisman, column 8, lines 12-18) and not ligated adapters (see, for example, Weisman, column 4, lines 57-58). The use of restriction sites in this way also teaches away from the use of a mutHL site, as the MutSLH system is said to “introduce a single-stranded nick” and would not “release” the DNA as found in column 3. See Weissman, column 1, lines 44-46. Finally, Weissman at columns 7-8, and Figure 1(a), cited by the Examiner (Office Action at page 8), relates to the creation of DNA libraries, and putting restriction sites in PCR primers as a means to ligate an adaptor specific to that restriction site overhang after the DNA library is amplified. Weissman, columns 7-8. The use of the restriction sites to ligate adapters to DNA libraries also teaches away from the use of the MutSLH system in adapters as it in Weissman as introducing only “single-stranded nicks”. Weissman, column 1, lines 44-46.

Accordingly, Applicants respectfully request that any rejections of claims 1-19 under 35 U.S.C. § 103(a) over Lin be reconsidered and withdrawn. Applicants submit that new claims 20-31 are free of the prior art.

If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please

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charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully Submitted,

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